REMARKS

Applicant thanks Examiners Bunner and Brumback for the telephonic interview on October 14, 2004. Claims 1-109 have been canceled. New claims 110-118 have been added. Support for the new claims can be found in the claims as originally filed and throughout the specification, for example at page 56, lines 5-11, page 58, line 30 through page 60, line 4, page 61, line 11, though page 62, and pages 68-70. No new matter has been added. Applicant reserves the right to file a divisional or continuing applications for the non-elected claims or to reinstate certain canceled claims.

Applicant respectfully request reconsideration of the application in view of the issues discussed in the telephone interview which are summarized in the remarks that follow.

Rejection of Claims 1-3, 5-8, 22-25, 27-28, 36-40, 54, 68, 86-90, 95-97, 102-104 and 109 under 35 USC §112, First paragraph

Claims 1-3, 5-8, 22-25, 27-28, 36-40, 54, 68, 86-90, 95-97, 102-104 and 109 have been rejected under §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Office Action states that:

> (i)....Although the experiments in the unpublished manuscript indicate that specific NMDARI antigens stimulate an immune response having anti-epileptic affects (seizure latency and progression) and protect against hippocampal cell death, the declaration is not persuasive. Specifically, *the NRI antigens (NRI[21-375], NRI [654-800]), the rat models of epilepsy, and other methods discussed by Dr. During and by the manuscript are not disclosed in the specification* of the instant application as originally filed. The specification provides no guidance or working examples for the administration of a NMDAR1 antigen peptide vaccine and modification of the function of any target receptor in a subject, particularly by utilizing NRI [21-375], NRI [654-800] and rat models of epilepsy.

The Office Action further states that:

> (ii)... There is little or no guidance provided in the specification that indicates *which specific neuronal cells have a desired target receptor* and are also associated with neurological disorders, a neuroendocrine disorder, or cognition...Undue experimentation would also be required of the skilled artisan

> to even determine which *region of the CNS* should be targeted with the antigen/antibodies (emphasis added).

Applicant respectfully traverses the rejection. Claims 1-3, 5-8, 22-25, 27-28, 36-40, 54, 68, and 102-104 have been canceled, thereby rendering the rejection moot with regard to these claims. Nonetheless, to the extent that theses grounds for rejection may be pertinent to new claims 110-118, Applicant notes that the new claims now specifically recite a method for modifying the function of an *N-methyl-D-aspartate receptor* associated with a neurological disorder in a *hippocampal region* of a subject.

As suggested by Examiner Bunner during the telephonic interview, Applicant's new principal claim (claim 110) further recites that the method is accomplished by administering a vaccine into the circulatory system of the subject comprising a therapeutically effective amount of *a peptide antigen derived from an N-methyl-D-aspartate receptor subunit 1 (NMDAR1)*. The peptide is derived from an antigenic region of the NMDAR1 selected from at least one of five specific regions identified in Applicant's specification. These regions are defined in claim 110 as a Markush group consisting of *the N-terminal extracellular domain, the preM1 region, the M4n region, the M3c region, and the extracellular loop between M3 and M4.*

New claim 110 further specifies that the antigen elicits the production of antibodies that pass into the central nervous system of the subject and interact with N-methyl-D-aspartate 1 receptors located on neuronal cells in the *hippocampus* of the subject.

During the telephonic interview, Applicant's previously-submitted declaration that addressed the enablement issue, was discussed at length. It was noted that the declaration included a manuscript entitled "Protein Vaccination Leading to a Preconditioned Phenotype Associated with resistance to Seizures and Neuroprotection," which demonstrated a reduction to practice of the invention. During the interview, the issue raised in the outstanding Office Action of whether Applicant's specification disclose the peptides used in the manuscript was addressed by Dr. During himself. It was noted that the antigen NR1 [654-800], which was shown in the manuscript to have therapeutic effects, embraced three of the claimed regions (the M3c region [641-657], the extracellular loop between M3 and M4 [681-696] and the M4n region [711-726].

For the Examiner's convenience, Table 1 outlines the various domains identified by Applicant in the specification (now recited in claim 110) and the corresponding experimental proof provided by the manuscript.

Table 1: Table showing peptides in the specification that are encompassed by the peptides in the manuscript

Peptide in the Application	Amino Acids in the Application	Rat Number	NMDAR1 Domain identified in the application	Peptide in the Manuscript
49	483-498	N19	N-terminal of M1	
55	541-566	N52	PreM1	
65	641-657	N11	M3c	NR1[654-800]
69	681-696	N21	Extracellular domain between M3 and M4	NR1[654-800]
72	711-726	N64	Extracellular domain between M3 and M4	NR1[654-800]
80	791-807		M4n	NR1[654-800]

It was further noted during the telephonic interview that each of five of the regions of NMDAR1 now recited in new claim 110 is enabled by the specification itself. Applicant clearly identified antigenic regions in NMDAR1 by epitope mapping experiments creating 94 overlapping 16mers to cover the entire 938 amino acid polypeptide of NMDAR1. (*See* pages 57 & 58). The specification identifies six of the 16mer peptides as antigenic. From these peptides, Applicant identified the domains of NMDAR1 that would raise antibodies.

The manuscript not only provides experimental proof for three of the five regions identified by Applicant, but also demonstrates the straightforward nature of practicing the invention. Contrary to the assertions in the Office Action, this is not a situation where guidance was insufficient or undue experimentation was required. As noted, Dr. During's experiments followed directly from the teachings of the specification.

During the telephone conference the issue of the animal models of epilepsy was also discussed. Applicant specifically disagreed with the assertion in the Office Action that the rat model described in the During declaration and manuscript was not the same as that described in the specification. Dr. During explained how the data in the manuscript followed the protocols described in the specification. It was noted that the specification describes how to induce epileptic seizure activity in rats by administering kainite four weeks after vector or vaccine administration. Specifically the specification states at page 58, line 8 that:

> At one month following vaccination, animals were administered 10 mg/kg kainic acid intraperitoneally and a blinded observer determined over 2 hours whether there were any signs of the characteristic progression through various behavioural seizure stages, including immobility and staring, 'wet-dog-shakes', facial clonus, unilateral and bilateral forelimb clonus (Sperk (1994) *Prog. Neurobiol.* 42:1).

Dr. During confirmed that this same model for epilepsy was used in the manuscript (*See* page 8):

> **Kainic acid induced seizure model: systemic administration.** 9 - 12 weeks after immunization, rats received a single i.p. dose of kainic acid (KA, BioVectra, Charlottetown, Canada;10mg/kg). Seizure activity was monitored over a 90 min period and scored...

In addition, it was noted that the manuscript also describes another model (*See* page 9):

> **Kainic acid induced seizure model: intrahippocampal administration.** 17 - 21 weeks post-vaccination, further subgroups of vaccinated and naïve rats were tested for neuroprotection using an intrahippocampal kainic acid model of epilepsy...bipolar recording electrodes ...were stereotaxically implanted into the right hippocampus....After a post-operative period of 1 week, kainic acid (0.04μg in 0.5μl) was administered via the cannula to an area 3mm below dura. EEG signals were recorded over a 2h period.

In sum, both the specification and the manuscript describe the same systemic animal model for producing seizures. The manuscript also describes an additional model for seizures where kainic acid is administered into a specific region of the brain.

With regard to the working examples, it was also noted during the interview that the Examiner was correct to the extent that the working examples provided in the specification were directed to nucleic acid vaccines of NMDA receptor. However, Dr. During explained that the guidance provided in the specification was broader than a nucleic acid vaccine and equally applicable to peptide vaccines. He explained that one skilled in the art would readily recognize a nucleic acid vaccine as simply one way of administering peptides.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. The Examiner is urged to telephone the undersigned Representative for Applicant in the event that such communication is deemed to expedite prosecution of this matter.

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Respectfully submitted,

By _____

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